R E M A R K S

At the outset, applicants and their attorneys with to thank the Examiner for the courtesy of the recent interview. The Examiner's careful attention to the application on that occasion is greatly appreciated.

By the present amendment, a needed editorial correction is made to the specification, and claim 1 is amended in the manner discussed in detail at the interview. This is the form of claim 1 which it is believed clarifies the recitation of the invention and underscores the patentable novelty of the invention relative to the applied prior art.

The sole issue remaining in this application is the rejection of claims 1-27 under 35 USC 103, as allegedly being unpatentable based on MASIZ U.S Patent No. 5,645,854 in view of ROBERTS et al. U.S. Patent No. 5,750,141, further considered with a series of five additional secondary references, namely AZRIA et al. 5,149,537, KISSEL et al. ("Tolerability and Absorption Enhancement of Intranasally Administered Octreotide by Sodium Taurodihydrofusidate in Healthy Subjects", *Pharmaceutical Research*, Vol. 9, No. 1, 1992, pp. 52-57), Japan 3-5427, EPA-215697, and COOPER U.S. Patent No. 4,557,934. That rejection is respectfully traversed, for the following reasons.

As was discussed at the interview, MASIZ describes the simultaneous administration of an active agent (which could be insulin), a vasodilator, and a permeation enhancer. However, MASIZ is not a good reference relative to the claimed

invention, in that it contemplates solely transdermal delivery, and therefore does not describe or suggest the claimed invention with its vasodilators and permeation enhancers suitable for transmucosal delivery.

Furthermore, there would have been no motivation to modify MASIZ, to include any of the particular vasodilators described by ROBERTS et al.

The remaining five references applied in the rejection are cumulative of the prior art described at pages 2-3 of the present specification, in that they describe conventional compositions for administering physiologically active peptides in conjunction with a permeation enhancer for transmucosal delivery, but with no vasodilator.

Indeed, as is described at page 4, lines 15-17 of the present specification, the present invention represents a radical departure from conventional compositions for transmucosal administration of physiologically active peptides, in that the use of vasodilators in this context had not previously been considered. The prior art relied upon in the outstanding Official Action discloses nothing to contradict that statement.

In particular, the Official Action sought to address the above-noted shortcomings of MASIZ, wherein at page 3, lines 4-7 of the Official Action the Examiner suggested that transmucosal delivery was indicated by the mention of activation via saliva in claim 16 of MASIZ.

However, as was discussed at the interview, a careful review of not only claim 16 but also column 5, lines 18-28 of MASIZ indicates that the mention of saliva in fact does not pertain at all to transmucosal delivery, but rather to the ambient to which the disclosed complex is delivered transdermally. That is, saliva is given as an example of a bodily fluid that can dissolve the water soluble gum which holds the MASIZ complex together; however, that dissociation occurs only after the complex has been delivered, and the transdermal route is the only delivery route disclosed or suggested.

Therefore, MASIZ simply does not fit with the other references applied in the proposed combination, wherein the latter five pertain to permeation enhancers selected for transmucosal delivery. Given the solely transdermal nature of the MASIZ delivery, there would have been no motivation to replace the transdermal permeation enhancers of the primary reference with any of the transmucosal permeation enhancers of the latter five secondary references.

The Examiner's reliance on claim 16 of MASIZ was thus a linchpin for maintaining the proposed obviousness rejection; however, when that claim is more fully considered together with its supporting disclosure at column 5, lines 18-28, it is apparent that the rejection cannot properly be maintained.

The Examiner also referred to the abstract of MASIZ for the proposition that an irritant is an optional ingredient

of the disclosed composition. While the abstract does use the phrase "a vasodilator and/or topical counterirritant", the full disclosure of the reference indicates that these terms are used interchangeably, and that the vasodilator used for the transdermal transport system of MASIZ is itself an irritant, in order to perform its intended transdermal function. The Examiner's attention in this respect is directed to the paragraph bridging columns 2 and 3 of the reference. Of course, agents which are topical irritants will be all the more irritating to mucosal tissue, and are plainly unsuitable for use in the present invention.

This further distinction between the invention and the applied prior art is emphasized in claim 1 as amended herewith, by the recitation that the vasodilator used in the claimed composition is one whose vasodilating activity occurs without mucosal irritation. As was discussed at the interview, that added phrase is well-supported by the specification as originally filed, in that the vasodilators described at pages 8-9 of the specification inherently possess the non-irritating nature on mucosal tissue. The recitation is further supported by the specification for example in the paragraph bridging pages 3 and 4, wherein at the top of page 4 it is specified that the claimed compositions operate without detrimental action on mucosa; and in the concluding paragraph on page 37 of the specification, wherein a similar disclosure appears.

Given that MASIZ describes a preparation that is solely for transdermal delivery of an active agent in the form of a water-soluble complex, there would have been no motivation to replace the MASIZ vasodilators, which necessarily have an irritant nature, with those of ROBERTS et al., which, in the present invention, necessarily lack that property.

From the above discussion, therefore, it is believed to be apparent that the rejection of claims 1-27 based on the proposed combination of the seven applied references, cannot properly be maintained. Favorable reconsideration and withdrawal thereof are accordingly respectfully requested.

In view of the recent interview and the present amendment and the foregoing remarks, therefore, it is believed that this application is now in condition for allowance, with claims 1-27, as amended. Allowance and passage to issue on that basis are accordingly respectfully requested.

Respectfully submitted,

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